INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL04/01046

A. CLASSIFICATION OF SUBJECT MATTER
IPC: C12N 5/00(20Q6.01),5/02(2006.01),S/06(2006.01),5/10(2006.0 1),5/08(2006.01),15/63(2006.01)
C12N 15/83(2006.0 1),15/87(2006.01)

USPC: 435/325,352,354,363,366,383,391 ,392,45 5
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/325,352,354,363,366,383,391,392,455

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	RATCLIFF, R. et al. Disruption of the Cystic Fibrosis Transmembrane Conductance Regulator Gene in Embryonic Stem Cells by Gene Targeting. Transgenic Research. July 1992, Vol 1, No. 4, pages 177-181.	1,2,4,5 ---------- 7-11
X --- Y	HKKE VAN DOORNINCK, J. et al. A Mouse Model for the Cystic Fibrosis DELTA-F508 Mutation. EMBO, 1995, Vol 14, No. 18, pages 4403-441 1.	1,2,4,5 ---------- 7-1 1
X --- Y	O'NEAL, W. et al. A Severe Phenotype in Mice with a Duplication in Exon 3 in the Cystic Fibrosis Locus. Human Molecular Genetics. 1993, Vol. 2, No. 10, pages 1561-1569.	1,2,4,5 ---------- 7-11
Y,P	WO 2004/072251 A2 (WISCONSIN ALLUMNI RESEARCH FOUNDATION.) 26 August 2004 (26.08.2004).	1-5,7-1 1

[/Kj] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
29 March 2006 (29.03.2006)

Date of mailing of the international search report
03 MAY 2006

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Form PCT/ISA/210 (second sheet) (April 2005)

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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ROACH, M. et al. Methods for the Isolation and Maintenance of Murine Embyonic Stem cells (Chapter 1), pages 1-16, from Methods in Molecular Biology, Vol. 18_5: Embryonic Stem Cells: Methods and Protocols. Ed. K. Turkesen, Humana Press Inc., Totowa, NJ, 2002.	1, 2, 4, 5, 7-1 1

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 6
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 6 is was not searched because no CRF was provided.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. **D** As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-5 and 7-1 1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

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BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1_{-5} and 7-1 1 drawn to isolated stem cells or stem cell lines carrying a disease-causing mutation in a genomic polynucleotide sequence thereof.

Group II, claim(s) 12-26, drawn to isolated embryoid bodies comprising a plurality of cells at least some of which carry a disease-causing mutation in a genomic polynucleotide sequence thereof.

Group III, claim(s) 27-34, drawn to isolated differentiated cells, tissues or organs, carrying at least one disease-causing mutation in a genomic polynucleotide sequence thereof.

Group rv, claim(s) 35-51, drawn to methods of identifying agents suitable for treating a disorder associated with at least one disease-causing mutation.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Unity of Invention between different categories of inventions will only be found to exist if specific combinations of inventions are present. Those combinations include:

1) A product and a special process of manufacture of said product
2) A product and a process of use of said product
3) A product, a special process of manufacture of said product, and a process of use of said product
4) A process and an apparatus specially designed to carry out said process
5) A product, a special process of manufacture of said product, and an apparatus specially designed to carry out said process.

The allowed combinations do not include multiple products, multiple methods of using said products, and methods of making multiple products as claimed in the instant invention.

The inventions are not so linked because they do not have a single general inventive concept. Groups I-III are to different products that are not required or recited for the implementation of the other. Bach of these products is distinct, both structurally and functionally, and thus, has its own special technical feature. Groups I-IV lack a common special technical feature, and thus, unity of invention is found to be lacking.

The special technical feature of Group I is considered to be an isolated stem cell or stem cell line, carrying a disease-causing mutation in a genomic polynucleotide sequence. The special technical feature of Group II is considered to be an isolated embryoid body comprising a plurality of cells, wherein at least some of which carry a disease-causing mutation in a genomic polynucleotide sequence. The special technical feature of Group III is considered to be an isolated differentiated cell, tissue or organ, carrying at least one disease-causing mutation in a genomic polynucleotide sequence. The special technical feature of Group FV is considered to be a method of identifying an ~igent-suitable-for-treating-a-disorder-associatod-with-at-least-one-disease-causing-mutation.

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Groups I-IV lack a common, special technical feature because stem cells carrying a disease-causing mutation in a genomic polynucleotide sequence were well-known in the art. For example, this is evidenced by Leonard *et al.* (Immunological Reviews, 148:97-1 14 (1995)) who teach a mutation in the γ_c gene in mice results in various abnormalities, with similar characteristics as seen in patients suffering from X-linked severe combined immunodeficiency. See Abstract. They teach that these mice were developed by transfection of mouse ES cells, and homologous recombination to produce the knockout ES cells. These ES cells were then used to produce the knockout mice. Thus, Leonard *et al.* show a stem cell that has a mutation that causes a disease in the resultant mouse.
Thus, Groups I-IV are not so linked by the same or a corresponding special technical feature as to form a single, general inventive concept.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

(a) Distinct types of mutations, recited in claims 4, 17, 32, 40.
- i) missense
- ü) nonsense
- iii) frameshift
- iv) readthrough
- v) promoter
- vi) regulatory
- vii) deletion
- viii) insertion
- ix) inversion
- x) splice
- Xi) duplication

Distinct disease-causing mutations, recited in claims 5, 6, 18, 19, 33, 34, 41, 42
- i) cystic fibrosis
- ü) myotonic dystrophy
- iii) van Waardenburg syndrome
- iv) metachromatic leukodystrophy
- v) Gorlin disease
- Vi) Huntington's disease
- vii) Spinal muscular atrophy
- viii) Duchenne muscular dystrophy
- ix) SEQ ID NO: 24
- x) 510del28 in SEQ ID NO: 34
- Xi) SEQ ID NO: 22
- xii) SEQ ID NO: 2 1

Continuation of B. FIELDS SEARCHED Item 3:
CAPLUS, MEDLINE, EMBASE, BIOSIS, LIFESCI, WEST
search terms: stem cell, mutation, disease, human